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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,183	11/14/2001	Alan Gewirtz	43826-9	6995

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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.**	**Applicant(s)**
	09/993,183	GEWIRTZ, ALAN
	Examiner	**Art Unit**
	Jon B. Ashen	1635

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 February 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered, ~~and an explanation of how the new or amended claims would be rejected is provided below or appended.~~

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,5,7-9,11,14 and 17-22*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____

13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant has requested reconsideration of the claims. Applicant's arguments have been fully considered but are not found persuasive for the following reasons: In regards to the outstanding rejection under 35 U.S.C. § 112 1st paragraph, written description, Applicant has argued that the written description requirement is viewed in light of the state of the art and the skill of the practitioner at the time the application was filed (pg. 3, 2nd paragraph) and that it is clear that the invention need not be described ipsis verbis for the purposes of written description but rather that what is needed is that the skilled artisan understand, based on the disclosure of the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor has possession of the claimed subject matter and that one skilled in the art, upon reading the specification, would have understood what was meant by an RNA that is homologous to any target gene and that thus, Applicant was in possession of the claimed invention (pg. 6, 4th and 5th paragraphs). This argument is not found persuasive for the reasons of record set forth in the prior Office Action which considers that the disclosure of the specification and the teachings of the prior art as a whole, fail to provide or point to the structure of an RNA that can have any degree of homology to any target gene, that is commensurate with what is claimed, that will provide the function of RNA interference to any cell. Applicant further argues that the degree of homology for the claimed invention is inherently disclosed in the examples of the specification and would have been recognized by one of skill in the art because the specification teaches the in vitro transcription of RNA from a DNA template that provides the sequence to which a homologous RNA is desired and the annealing of this RNA to form dsRNA (pg. 6, last paragraph bridge to pg. 7). Applicant then presents arguments concerning the error rates of RNA polymerases. However, it is not clear how this argument addresses the outstanding grounds of rejection. Applicants arguments do not provide or point to the structure of an RNA wherein that RNA can have any degree of homology to any target gene, that is commensurate with what is claimed, that will provide the function of RNA interference to any cell. Applicant further argues that the specification provides teachings on the length of the dsRNA homologous to a target gene because the specification provides an example of a dsRNA molecule that is 828 bp long, therefore providing an upper limit on what sized dsRNA is successfully used in the method as claimed (pg. 7, last paragraph) and that the lower limit on the size of the dsRNA is evident in the logic used in designing antisense molecules and that one skilled in the art recognizes that the minimum dsRNA size to achieve target specificity is 17 nucleotides. (bottom of pg. 7 bridge to pg. 8). This argument is not persuasive because examples drawn from Applicant's specification are exemplifications of the claimed invention and the instant claims are not limited to the subject matter as exemplified by Applicant. In regards to the minimum size of a dsRNA molecule, Applicant's arguments again fail to address the outstanding grounds of rejection in that they provide or point to no particular structure of an RNA that functions to initiate RNA interference. In summary, Applicant has argued that the specification teaches the degree of homology for the dsRNA used in the claimed invention as well as the size ranges for the dsRNA and the methof of making dsRNA homologous to the target gene and that based on the disclosure and the knowledge of the skilled artisan at the time, a skilled artisan would understand that applicant had sposession of the claimed subject matter (pg. 9, 1st paragraph). However, this argument is not found persuasive. Applicant has pointed to the Regents of the University of California v. Eli Lilly wherein the Court of Appeals for the Federal Circuit stated: "in claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." However, an analysis of the facts in the instant Application indicates that although the state of the art recognizes a general formula for RNA, in that it is comprised of 4 types of nucleobases, the state of the art recognizes that what distinguishes one RNA from another RNA is the fact of primary nucleotide sequence. Without such primary nucleotide sequence information, there is no way for one skilled in the art to distinguish one RNA from another RNA such that one skilled in the art can identify many of the species that the claims encompass.

In regards to the outstanding rejection under 35 U.S.C. § 112 1st paragraph, enablement, Applicant's arguments have been fully considered but are not found persuasive for the following reasons. Applicant has presented arguments that were previously presented in the communication filed 7/15/2004, that the present specification, including the working examples, contains ample direction on how to practice the full breadth of the claimed RNAi therapeutic method (pg. 10, 2nd and 3rd paragraphs). These arguments are not found persuasive for the reasons of record set forth in the prior Office Action. Applicant has also argued that two of the references cited by the Examiner discuss the various successful ways nucleic acid is delivered in vivo to cells. Although Applicant is correct in pointing out that the abovementioned references do discuss the various successful ways nucleic acid can be delivered in vivo, to cells, neither of these references, taken as a whole, and as set forth in the prior Office Action, considers that the uptake and biological activity observed in vitro will predictably translate to in vivo results, in part, at least, because formulations and techniques for delivery in vitro are often not applicable in vivo. Applicant further argues that recent work has shown that dsRNA can be successfully delivered in vivo using intravenous delivery methods as taught in the specification because the specification generally contemplates intravenous administration. However, Applicant's contention that these references make it clear that undue expermentation is not necessary to carry out Applicant's invention is not persuasive because the determination of an enabling disclosure is made at the time of filing. These references were published several years after the filing of the instant application and therefore indicate that, at the time the instant invention was made, the state of the art nucleic acid therapeutics still required several years for the enablement of even a small number of nucleic acid therapeutics in vivo.

In regards to the outstanding rejection under 35 U.S.C. § 102(e) as being anticipated by Fire et al. (US 6,506,559), applicants arguments have been fully considered but are not found persuasive. Applicant has argued that reduction to practice in the Fire specification is limited to the invertebrate animal, C. elegans and that the disclosure regarding dsRNA induced inhibition in higher order, vertebrate cells, was sheer speculation. However, as pointed out by Applicant in the instant response, reduction to practice is not required for a specification to be enabling. The Fire reference is a patent. The rejection under Fire is a rejection under claims in an issued patent, the enablement of which is presumed valid. Applicant argues that Fire, in papers authored after the filing date of US 6,506,559, makes clear the speculative nature of RNAi in mammalian cells and provides 2 quotations. However, the references alluded to by Applicant are not of record in the application file and were not provided by Applicant in this response. Therefore, because the Examiner cannot make assumptions about what is contained within these references, as a whole, arguments drawn to specific statements taken out of context from these references are not considered persuasive. It is noted herein that submission of the abovementioned references with Applicant's instant response could be precluded under 37 C.F.R. 1.195. Should Applicant wish the abovementioned references to be considered, Applicant may

wish to submitt such with any request for continued examination.

SEAN McGARRY
PRIMARY EXAMINER
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